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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,372	ADEMA, ENNO	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008 and 14 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *3 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed in the corrected Reply of 8/14/08, is acknowledged and has been entered. Claim 1 was amended. Claims 1-11 remain pending in the application, with claims 3 and 5 currently withdrawn. Claims 1-2, 4, and 6-11 are subject to examination below.

Priority

2. The present application was filed on 8/29/2003 and claims foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 102 39 821.6, filed on 8/29/2002 in Germany.

Objections/ Rejections Withdrawn

3. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

Information Disclosure Statement

4. The information disclosure statement filed 5/22/08 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

In particular, the non-patent literature publication by Witt et al. and Japanese patent No. 10-17549 have not been considered because the references are not in English and no explanations of relevance were provided.

Furthermore, the publication of Lill et al. has been considered to the extent possible; but the citation to Lill et al. has been lined through on the said IDS because no date was provided therein, the fact of which could result in a printer rush.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 4, and 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

7. Claim 1, as instantly amended, recites that the first reagent R1 comprises an "**excess**" of AT binding partner. Support for the noted limitation could not be found in the specification, and Applicant's Reply does not indicate where support may be found. Furthermore, it is not apparent what the "excess" of AT binding partner is relative to (see rejection under 112, 2nd paragraph below). As such, the claim would encompass methods in which the AT binding partner is present

in an amount or degree that is greater than that of the R2 reagent; in an amount or degree greater than that of the R3 reagent, greater than that of antithrombin III or interfering factor in the sample, etc.[1] Such embodiments are not discussed in the specification. Alternatively, the claim would encompass methods in which the amount of AT binding partner exceeds proper or usual limits. However, the specification does not describe what such proper or usual limits might be. For all of these reasons, one skilled in the art cannot envisage possession of the claimed methods.

8. Claim 1, as instantly amended, now recites in part (a) that "a portion of the AT binding partner interacts with the interfering factor **such that the interfering factor is no longer available to interfere with the AT**". Support for the noted limitation could not be found in the specification or claims as originally filed, and Applicant's Reply does not indicate where support may be found.

The specification discloses at [0004] that interfering factors can interact with thrombin and result in false high AT values. This would suggest that the interfering factors interfere with assays to measure AT. However, the specification does not disclose that interfering factors interfere with AT *per se*. This could imply, for example, that the interfering factors bind to and/or inhibit AT. Such concepts are not clearly described in the specification, and one skilled in the art would not envisage interfering factors that bind to AT based on the disclosed examples of inhibitors of thrombin. The disclosure of thrombin inhibitors fails to convey evidence of possession of interfering factors that can "interfere" with AT.

[1] See the attached definition for the term "excess", Merriam-Webster's Online Dictionary, retrieved from http://www.merriam-webster.com/dictionary/excess[1] on 10/18/08.

Written Description

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...") *Regents of the University of California v. Eli Lilly & Co,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of

representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims recite a method for detecting antithrombin III (AT) in a sample that main contain an "**interfering factor**" using three reagents, R1, R2, and R3.

The claimed reagents encompass a genus of molecules not adequately described by the specification. Similarly, the claims invoke a genus of "interfering factors" that are not adequately described.

Regarding the first reagent R1, the claims require that the reagent comprise an "**AT binding partner**" and must also be able to interact with an interfering factor under certain conditions, but interact with AT in response to addition of a third reagent R3.

The specification discloses thrombin and factor Xa as examples of suitable AT binding partners [0011] (see also dependent claims 2-3). However, the specification does not identify any shared partial structure shared by the R1 reagents. As such, the genus has not been identified by a precise definition, but only by reference to desired functional characteristics. Further, the specification does not disclose what structures would be responsible for the desired functional characteristics (binding to AT and "interfering factor"). Absent a disclosed correlation between

structure and function, one skilled in the art would not envisage possession of the genus of R1 reagents based on the disclosure of the two species thrombin and factor Xa.

Regarding the second reagent **R2**, Applicant claims any reagent "for a first determination of the free fraction of the AT binding partner". The specification discloses peptidic chromogenic substrates that are acted on by thrombin [0012] as well as antibodies [0009]. However, the specification does not disclose what structural characteristics of these reagents are responsible for their function. Accordingly, the disclosure of a limited number of species fails to adequately identify the claimed genus drawn to all reagents for determining the free fraction of the AT binding partner.

Furthermore, as discussed above the "AT binding partner" is also not adequately described. Therefore, while Applicant has disclosed a limited number of reagents for determining the free fraction of *thrombin,* one skilled in the art would not envisage possession of methods of determining the free fraction of any AT binding partner. Applicant is attempting to describe an unknown by reference to another unknown.

Dependent claim 4 recites a "chromogenic substrate"; however, there is nothing in the claims that would require that the chromogenic substrate be a substrate of thrombin. Given that not all chromogenic substrates would be cleaved by thrombin to produce a color change, one skilled in the art would not envisage possession of methods in which R2 was any type of chromogenic agent.

Regarding the third reagent **R3**, which changes the conditions of the reaction mixture such that the AT binding partner interacts with AT, the specification discloses the single example of heparin [0014]. Claim 6 also requires that the third reagent R3 contain an "accelerator" of the

interaction between AT and the AT binding partner. The specification does not disclose any partial structure or physical and/or chemical properties shared by the members of the genus of R3 reagents. There is no disclosed correlation between structure and the necessary functions.

Therefore, while methods involving the use of *heparin* are adequately described (as in instant claim 7), one skilled in the art would not know, based on the specification, what other molecules or compounds would possess the necessary functional characteristics of accelerating or changing the reaction conditions as recited. Indeed, while it is known in the art that heparin potentiates the antithrombin activity of AT by enhancing the rate of formation of the thrombin:AT complex, this specific example fails to convey evidence of possession of all reagents that act in a similar manner to enhance the rate of formation of AT with any "AT binding partner".

With respect to claim 10, the recitation of an "**additional AT binding partner**" as part of the third reagent R3 is also not adequately described for similar reasons as discussed above with respect to the first reagent R1.

Similarly, although the specification discloses *polybrene* as a reagent that is an antagonist for *heparin,* the specification does not disclose sufficient characteristics to identify the genus of *antagonists for accelerator of the interaction between AT and AT binding partner* as in instant claim 8. One skilled in the art would not know what other reagents besides polybrene might be capable of antagonizing accelerators as required by the claims.

Finally, the claims refer to a sample that may contain an "interfering factor" that interacts with an AT binding partner under certain conditions. However, apart from thrombin inhibitors

such as hirudin, the specification does not disclose what other "interfering factors" would be able to bind to AT binding partners under certain conditions and not others.

Absent sufficient recitation of distinguishing identifying characteristics, the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

9. Claims 1-2, 4, and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Step (b) of claim 1 recites the step of adding a second reagent R2 “for a first determination of said first fraction of the binding partner”. This language renders the claim indefinite because it may be interpreted as referring simply to the intended use of the second reagent R2 and does not make clear whether a first determination is actually performed in this step or not.

11. The term "excess" in claim 1 is a relative term which renders the claim indefinite. The term "excess" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Step (a) of claim 1 recites a first reagent R1 that comprises an "excess" of AT binding partner, which implies that this reagent is being provided in an amount or degree that exceeds another reagent (see the attached definition for the term "excess" by Merriam-Webster's Online

Dictionary). However, the specification and claims do not indicate what other reagent or reagents the "excess" is meant to be relative to. Alternatively, an "excess" could refer to surpassing of usual, proper, or specified limits. However, the specification and claims do not indicate what would be considered usual or proper amounts of AT binding partner, and no limits are specified. For all of these reasons, the claim is indefinite because there is no frame of reference for understanding the term "excess". An excess as compared to what?

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-2, 4, 6-7, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. (US 4,219,497) in view of Furatu (EP 0 041 366), Morris et al. (US 4,314,987), and Akhavan-Tafti et al. (US 6,068,979).

Plattner et al teach a method of measuring total AT-III activity by taking advantage of the fact that AT-Ill inhibits human (z-thrombin and heparin potentiates the activity of AT-Ill, wherein it is possible to delineate the inhibition of thrombin by AT-III from other plasma proteins (i.e. thrombin essentially does not interact with AT but interacts with interfering factor) by measuring a reaction mixture between thrombin and a chromogenic substrate (i.e. adding a second reagent R2; suitable for immunological determination) through measuring total AT-III as an entity (i.e. adding third reagent R3 to change the conditions such that the AT binding partner

interacts with AT and conducting a second determination of free fraction of AT binding partner; R3 separate from R1) distinct from the "progressive anti-thrombin activity" measured in the absence of heparin (i.e. first determination of free fraction of AT binding partner), such that the amount of AT-Ill and the amount of color produced from the substrate cleavage by thrombin are inversely proportional, and the level of AT-Ill can therefore be readily determined (i.e. determining the AT content in the sample from the difference between the first and second determinations of the free fraction of thrombin; kinetic determination). See column 6, line 28 to column 7, line 6. The reagent R1 (thrombin) is present in excess (see equations spanning column 6, lines 40-50).

Thus, the reference teaches determining total AT-III activity (in which case the measurement occurs in the presence of heparin) as well as progressive anti-thrombin activity (in which case the measurement occurs in the absence of heparin). Both of these measurements are performed by detecting thrombin activity on a chromogenic substrate as instantly claimed.

Plattner et al. differs from the claimed invention in that it fails to specifically teach conducting these two measurements in a single reaction mixture. In other words, Plattner et al. teach performing the claimed determination steps *in parallel*, while the instantly claimed invention requires that they be performed *sequentially*, on the same sample or reaction mixture.

However, it was known in the art to subject a single sample to multiple measurements in sequence. For example, Furatu et al. teach subjecting a sample to a plurality of reactions sequentially (see especially pages 1-4). In one embodiment, a reagent solution containing an enzyme is added to a sample solution to cause enzyme reaction, and the result is determined by colorimetric detection (page 3, the first paragraph). Next, a second reagent solution is added to

the first reagent solution and a second detection step is performed (page 3, the last paragraph to page 4, first paragraph).

Furatu et al. teach that one advantage in performing a plurality of measurements on a single sample is that only a very small amount of a sample is used, which decreases the sampling number and omits the need for successive sampling operations (page 2).

Morris et al. teach performing a continuous sequence of tests in time on the same blood sample in order to avoid numerous errors that may be introduced by delays in time, differences in blood samples, etc. (column 3, lines 32-53).

Akhavan-Tafti et al. teach that it is frequently desirable to be able to detect and/or quantify more than one analyte at a time in a single test system; savings in time, reagents and materials can thereby be realized and assay protocols can be simplified (column 1, lines 55-63). The solution proposed by Akhavan-Tafti involves sequential detection (see especially the title and abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to detect thrombin activity in the absence and in the presence of heparin as taught by Plattner et al., but to perform these two measurements *sequentially* in the same reaction mixture rather than in parallel. Performing multiple measurements on a single sample was known in the art, as taught for example by Furatu et al., Morris et al., and Akhavan-Tafti et al. Although these references do not relate to determination of AT-III specifically, given that the chemistry of AT-III/thrombin reaction were well established at the time of the invention (as taught for example in Plattner et al.), it would have been further obvious to perform the measurement of "progressive anti-thrombin activity" in the absence of heparin first, and to then add heparin for determination of

total AT-III activity (thereby changing the reaction conditions as recited). Put another way, it would have been obvious to use known techniques to improve upon known methods in which multiple measurements are performed, such as those of Plattner et al.

One would be motivated to perform the measurements sequentially on a single sample in order to minimize the amount of sample required, in order to save time, reagents, and materials, in order to simplify assay protocols, and/or in order to reduce errors due to delays in time and/or differences in blood samples.

14. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claims 1 and 6-7 above, and further in light of the evidence of Gitel et al. (US 4,883,751).

The references are as discussed above. Plattner et al. teaches measurement in the presence of *heparin* (i.e., reagent R3), but fails to specify whether heparin is an AT binding partner.

Gitel et al. provides evidence that heparin is an AT binding partner (column 1, line 23). Therefore, when performing the method of Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. as discussed above, it would have been obvious to arrive at the claimed invention because heparin (as taught by Plattner et al.) is an AT binding partner (as evidenced by Gitel et al.).

15. Claims 8-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Exner (US 6,051,434).

The Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fail to specifically teach that the first reagent R1 comprises polybrene.

Exner teaches a mixture including polybrene, in order to reverse the effect of any heparin that may be present in test samples. See column 3, lines 34-37. It would have been obvious to one of ordinary skill in the art at the time of the invention to include polybrene, as taught by Exner, in the step of measuring the progressive anti-thrombin activity, as taught by Plattner et al, in order to reverse the effect of any heparin that may be present in test samples. Since the measurement step of Plattner et al requires determining the activity of anti-thrombin in the absence of heparin, the inclusion of polybrene would ensure the success of the assay, thereby providing motivation to combine Plattner et al and Exner references. In addition; one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the polybrene of Exner in the method of Plattner et al. Furatu, Morris et al., and Akhavan-Tafti et al., since Plattner et al teach measurement steps excluding thrombin:AT-III interaction, and the polybrene of Exner is well known in the art as capable of preventing the effect of heparin on inducing thrombin:AT-III complexes.

16. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Nesheim et al (US 5,308,755).

The Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fails to specifically teach an additional AT binding partner.

Nesheim et al teach the addition of purified Factor Xa, in order to perform a competition assay with heparin for antithrombin III to determine the level of heparin activity. See column 2, line 51 to column 3, line 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Plattner et al., Furatu, Morris et al., and Akhavan-Tafti et al. with the addition of purified Factor Xa, as taught by Nesheim et al, in order to perform a competition assay with heparin for antithrombin III to determine the level of heparin activity. Determining the level of heparin activity, as taught by Nesheim et al, would indicate the extent of interaction heparin has with the relationship between thrombin and antithrombin III, as taught by Plattner et al, thereby providing the motivation to combine Plattner et al and Nesheim et al references. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the step of Nesheim et al in the method of Plattner et al, since both Plattner et al and Nesheim et al teach homogenous assays that include heparin and antithrombin II1.

Response to Arguments

17. Applicant's arguments filed 8/14/08 have been fully considered.

18. With respect to the rejections under § 112, 1st paragraph (written description), Applicant's arguments (Reply, pages 4-6) have been fully considered but are not persuasive.

Applicant argues that "[a]ny reagents that perform the stated functions, whether now known or to be discovered in the future, will be understood by those skilled in the art to be suitable" for the claimed methods (Reply, page 4).

This is not found persuasive because one cannot describe what one cannot conceive. Applicant points to as-yet discovered reagents, the structures of which cannot be envisaged by the skilled artisan. MPEP 2163 states:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

In the instant case, the specification discloses chromogenic assays to detect antithrombin III (AT) using thrombin as a binding partner. It was known in the art to conduct chromogenic assays for AT using thrombin. It was also known in the art to employ heparin in such assays, as heparin was known to potentiate the interaction between thrombin and AT.

However, although the thrombin-AT-heparin system was known in the art, it is not known what other molecules might exhibit the same particular binding characteristics. In particular, the claims are not limited to the use of thrombin, but invoke any first reagent R1 that "essentially does not interact with AT" under certain conditions but is later able to interact with AT upon addition of a third reagent R3. Although Applicant has described *thrombin* as a species reading on this claimed genus, the structural characteristics are common to other AT binding

partners falling within this genus cannot be envisaged. In particular, it is not known what other reagents might bind to AT under certain conditions but not others in the same manner as thrombin.

Likewise, although *heparin* was known in the art to potentiate the binding between thrombin and AT, Applicant has not adequately identified what other reagents might also possess this necessary functional characteristic, and therefore has not adequately described the genus of third reagents R3.

Similarly, the claimed methods invoke the use of a genus of "interfering factors". Although examples of interfering factors are suggested in the specification (e.g., drugs such as hirudin that can interact with thrombin), there is no disclosed correlation between structure and function. It is maintained for reasons of record that the identification of the genus of "interfering factors" only by reference to desired functional characteristics (i.e., ability to interact with AT binding partner under certain conditions) is insufficient. It is not known what other types of molecules might interact with thrombin (or other AT binding partners) under certain conditions but not others.

Applicant further argues that Applicant is not claiming the reagents *per se* but rather a method of using the reagents (Reply, page 5). This is not found persuasive because a disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product. Although examples of reagents R1, R2, and R3 are disclosed, the disclosure of particular species in this case would not lead one to the genera claimed, since there is insufficient information disclosed regarding what other reagents would also possess the necessary functional characteristics as those particular reagents disclosed.

Regarding the second reagent R2, Applicant further argues that chromogenic substrates were well known in the art (Reply, pages 5-6). This is not found persuasive because the claims are not limited to chromogenic substrates. Further, while the specification discloses certain chromogenic substrates that would possess the necessary functional characteristics for determination of AT, i.e. those chromogenic substrates that *are peptidic substrates of thrombin*, the claims broadly encompass all chromogenic substrates. Applicant points to the references by Fareed and Abilgaard; however, these references relate only to *peptide* chromogenic substrates that are cleaved by thrombin, and therefore fail to describe the claimed genus which encompasses both peptidic and non-peptidic chromogenic substrates.

It is apparent that not all chromogenic substrates would be capable of possessing the functional characteristics necessary for determination of AT. One skilled in the art would not envisage possession of using *any* chromogenic substrate in the claimed methods because with the exception of peptidic chromogenic substrates that are capable of being cleaved by thrombin, it would be unpredictable which substrates would produce a signal correlated to the amount of AT binding partner in the sample.

Applicant further argues that those skilled in the art would understand the scope of the reagents R1, R2, and R3 (Reply, page 5, last paragraph). Such arguments are not on point as they appear to be directed to issues of definiteness of terminology rather than written description.

19. With respect to the rejections under § 112, 2nd paragraph, Applicant argues that the amendments have obviated the grounds of rejection (Reply, page 6), to which the Examiner disagrees for reasons of record as set forth above.

20. With respect to the rejections under § 103, Applicant's arguments (Reply, pages 6-8) have been fully considered but are not persuasive.

Applicant argues that Plattner et al. does not teach conducting two measurements of the same substance at different times in a single reaction mixture (Reply, page 7). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further argues that Furatu does not teach analysis of a single substance by two separate measurements in a single reaction mixture; that Morris does not teach taking the difference between any two tests to determine a particular analyte; and that Akhavan-Tafti teaches taking the measurements of two different analytes rather than a single analyte at different times (reply, page 7).

This is not found persuasive for reasons of record. From the teachings of Furatu, Morris, and Akhavan-Tafti et al., it is evident that those of ordinary skill in the art appreciated the advantages of performing multiple *measurements* on a single sample. It would have been obvious to combine such teachings with those of Plattner et al., in which multiple measurements of thrombin activity were conducted, by performing the multiple measurements of thrombin activity in a single sample. One would have been motivated to combine the reference teachings in this manner because performing multiple measurements on a single sample was known in the

art to save time, reagents, and materials, simplify assay protocols, and/or in order to reduce errors due to delays in time and/or differences in blood samples.

Applicant further argues that the Examiner has provided only an open-ended statement that does not state how the references would be combined (Reply, page 7). However, the statement quoted by Applicant appears at the end of a paragraph that discusses the particular combination suggested by the reference teachings. Applicant is referred to the entire analysis as stated in the rejection of record, and in particular the entire paragraph that includes the quoted sentence.

Applicant further points to a non-patent literature publication by Hickey and argues that the reference shows that the problem of the drug Leprudin as an interfering factor in determinations of AT still had not been solved (Reply, paragraph bridging pages 7-8).

As best understood, Applicant argues that the claimed invention satisfied a long-felt need. MPEP 716.04 states that the relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors, one of which requires that the problem be one that has not already been solved:

> Second, the long-felt need must not have been satisfied by another before the invention by applicant. Newell Companies v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do-it-yourself" window shade material which was adjustable without the use of tools, a prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved".)

In the instant case, although the Hickey monograph indicates that patients under therapy with the thrombin inhibitor Lepirudin demonstrated slightly higher values in Hickey's *Innovance*

assay, Applicant has not advanced sufficient evidence to show that this problem was not already solved by others before invention by Applicant. To the contrary, the specification discloses that:

> A disadvantage of known methods for detecting AT by adding thrombin is that a false high AT value is obtained in the presence of interfering factors, e.g., drugs such as hirudin that can themselves interact with thrombin. This disadvantage can be avoided by using activated factor Xa instead of thrombin.

Therefore, Applicant's arguments that the claimed invention solved a long-felt need (that of drug interference in antithrombin III assays) are insufficient to outweigh the evidence of obviousness because here, the evidence of record indicates that the purported long-felt need was previously satisfied by others, as an alternative solution to this problem was already known.

Conclusion

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Mark L. Shibuya/
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